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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,478	07/29/2002	Kevin Jeffrey Barnham	113122.120	8704

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EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,478	BARNHAM ET AL.	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *1-30,37 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-36,38-42 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/26/02,3/27/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II (claims 31-42 and 44) and the species BRI 7158 (NiTPP-VLFFA; page 26), in the reply filed on January 10, 2006 is acknowledged. The traversal is on the ground(s) that the invention is drawn to a single general inventive concept and should be examined in the same application. Applicant asserts that, "the present application is predicated in part on the determination that zinc and copper bind predominantly to a region in the N-terminal loop of Aβ that includes a cluster of histidine residues." (page 4, *Remarks*).

This is not found persuasive because as shown in the restriction requirement, a *prima facie* case that unity of invention does not exist because the technical feature is not a contribution over the art. As stated previously, Shao (July 26, 2002 PTO-1449, reference A5) teaches that, "As for the nicotine-inhibition to β-amyloidosis, the NMR work established that nicotine binds to the His13 and His14 side-chains of the Tyr10-Val24 α-helix, and this prevented an α-helix → β-sheet conversion and β-amyloid precipitation." [*citation removed by Examiner*] (page 767).

Binding of nicotine to β-amyloid protein at His13 and His14 inherently 'blocks' the N-terminus in such a way that binding of metal ions at said His residues is/are inhibited, thus the technical feature is not a contribution over the art and the claims lack unity. There is no single general inventive concept, as unity of invention does not exist.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-30 and 43 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the reply filed on January 10, 2006.

Applicant's elected species was found to be free of the prior art for the instant claims, notwithstanding the rejections under 35 USC § 112, below. The examiner extended the search as set forth below, specifically practicing the claimed methods with the species nicotine and the compounds identified in FINDEIS (US Patents 5,854,215 and 5,817,626 and WO 96/28471 A1), e.g. biotin-Aβ(1-40). The species read upon **claims 31-36, 38-42 and 44**, which have been examined on the merits, and therefore **claim 37** is withdrawn from further consideration.

Sequence Compliance

Applicant is advised that the application is not in compliance with 37 CFR §§ 1.821-1.825.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR §§ 1.821- 1.825) in order to effect a complete response to this office action.

> 37 CFR § 1.821 (a) states,
> "Nucleotide and/or amino acid sequences as used in §§ 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Branched sequences are specifically excluded from this definition. Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. "Specifically defined" means those amino acids other than "Xaa" and those nucleotide bases other than "n" defined in accordance with the World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25: Standard for the Presentation of Nucleotide and Amino Acid Sequence Listings in Patent Applications (1998), including Tables 1 through 6 in Appendix 2."
>
> (a)(2) states,
> "*Amino acids*: Amino acids are those L-amino acids commonly found in naturally occurring proteins and are listed in WIPO Standard ST.25 (1998), Appendix 2, Table 3.

Those amino acid sequences containing D-amino acids are not intended to be embraced by this definition. Any amino acid sequence that contains post-translationally modified amino acids may be described as the amino acid sequence that is initially translated using the symbols shown in WIPO Standard ST.25 (1998), Appendix 2, Table 3 with the modified positions; e.g., hydroxylations or glycosylations, being described as set forth in WIPO Standard ST.25 (1998), Appendix 2, Table 4, but these modifications shall not be shown explicitly in the amino acid sequence. Any peptide or protein that can be expressed as a sequence using the symbols in WIPO Standard ST.25 (1998), Appendix 2, Table 3 in conjunction with a description in the Feature section to describe, for example, modified linkages, cross links and end caps, non-peptidyl bonds, etc., is embraced by this definition."

Specifically, the specification recites sequences which require sequence identifiers (SEQ ID NO), including the pentapeptide LVFFA at page 24, line 8 and KLVFFA at page 19, line 35.

Additionally, sequences represented as structures are embraced by this requirement, as well.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (<http://www.uspto.gov/ebc/efs/downloads/documents.htm>, EFS Submission User Manual – ePave)

2. US Postal Service:
Commissioner for Patents
PO Box 22313-1450
Alexandria, VA 22313-1450

3. Hand carry, Federal Express, United Parcel Service, or other delivery service:
U.S. Patent and Trademark Office
Mail Stop Sequence
Customer Window, Randolph Building
401 Dulany Street
Alexandria, VA 22314

Specification

The disclosure is objected to because of the following informality:

Sequences are recited without an accompanying SEQ ID NO.

Appropriate correction is required.

Please note, the lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claims 41 and 44 are objected to because of the following informalities: The claims depend from claims which are withdrawn from consideration. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41, 42 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Alzheimer's disease, does not reasonably provide enablement for prevention or alleviation of Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to methods of treatment, alleviation or prevention of Alzheimer's diseases via administration of a compound that generically inhibits binding of metal ions to Aβ or inhibits aggregation of Aβ. Thus, the claims taken together with the specification imply that administration of any compound that inhibits binding of metal ions to Aβ or inhibits aggregation of Aβ will treat, prevent or cure Alzheimer's disease.

Please note that for this rejection, the broadest reasonable interpretation of 'alleviate' encompasses 'to cure', as 'treat' has been specifically delineated in the text of the claim.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the art with regards to treating Alzheimer's is unpredictable.

WebMD (WebMD Alzheimer's Disease: treatment overview. Web document <http://my.webmd.com/content/article/71/81399.htm> Accessed 2/22/05. 2 pages) teaches that, "there is no cure for Alzheimer's disease and no proven way of slowing its progression. Because the exact cause of Alzheimer's disease is unknown, there is also nothing that can be done to prevent it." (page 1 of 2).

WebMD teaches that the approved drugs for treatment, "Aricept®, Exelon®, Reminyl®, and Cognex® seem to help only those with mild or moderate symptoms of Alzheimer's disease; Namenda® is prescribed for patients who have moderate-to-severe Alzheimer's." (page 2 of 2). The approved drugs are all for slowing the breakdown of acetylcholine.

Further, ADEAR (ADEAR Alzheimer's Disease Medications fact sheet. NIH Publication 03-3431. Alzheimer's Disease Education & Referral Center. National Institute on Aging, NIH, US Dept HHS. July 2004. 6 pages) teaches that Aricept®, Exelon®, Reminyl®, and Cognex® are for mild to moderate Alzheimer's disease (column 2), and Namenda® is for moderate to severe Alzheimer's (column 3).

Although these compounds are approved for treating Alzheimer's, Ballard (C Ballard, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease : randomized double blind placebo controlled trial. British Medical Journal. (2005) February 18, 5 pages) teaches that rivastigmine (Exelon®, *supra*), "seemed of no benefit in patients with dementia and agitation in institutional care," and that qeutiapine "was associated with greater cognitive decline that placebo." (page 4 of 5).

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided compounds asserted to be useful in the methods. The specification provides *in vitro* testing and *ex vivo* (e.g. NMR) testing for several compounds. However, the specification does not provide examples, working or prophetic, to show that any of the compounds work in treating, preventing or curing Alzheimer's.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above- particularly with regards to the high unpredictability in treating Alzheimer's disease, the unknown cause, the lack of knowledge in the prevention and/or cure of Alzheimer's, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation

to practice the method commensurate with the scope of the claims to prevent or cure (alleviate) Alzheimer's disease with the myriad of compounds embraced by the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-36, 38 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by SHAO.

The instant claims are drawn to inhibiting binding of metal ions or preventing Aβ aggregation (amyloidosis).

Shao teaches that, "As for the nicotine-inhibition to β-amyloidosis, the NMR work established that nicotine binds to the His13 and His14 side-chains of the Tyr10-Val24 α-helix, and this prevented an α-helix → β-sheet conversion and β-amyloid precipitation." [*citation removed by Examiner*] (page 767).

Thus, in conducting the NMR, one is inherently practicing the method, as binding of nicotine to β-amyloid protein at His13 and His14 inherently 'blocks' the N-terminus in such a way that binding of metal ions at said His residue(s) is/are inhibited.

Furthermore, because nicotine meets the requisite structural characteristics of claim 31, it necessarily must possess the same function, e.g. binding to specific sites on the Aβ protein, specific inhibition of various cations, etc. Additionally, because nicotine binds to Aβ it necessarily must 'comprise' a targeting moiety.

Claims 31-36, 38-42 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by NORDENBERG (T. Nordenberg. "It's Quitin' Time: Smokers Need Not Rely on Willpower Alone." FDA Publication 99-1288, May 1999, 6 pages) as evidenced by SHAO, *supra*.

The instant claims are drawn to inhibiting binding of metal ions or preventing Aβ aggregation (amyloidosis) and to methods of treating, preventing or alleviating (curing) Alzheimer's disease.

The teachings of Shao are presented *supra*.

Nordenberg teaches that, "The nicotine in cigarettes can command both a physical mental hold that can be tough to overcome." (page 1).

Nordenberg teaches that other nicotine products are approved by the FDA to quit smoking, including nicotine gum, nicotine patch, nicotine nasal spray and a nicotine inhaler (e.g. pages 1, 2 and esp. pages 4 and 5). "Like cigarettes, the products deliver nicotine into the blood..." (page 2).

Thus in any of the methods, smoking or attempting to quit smoking, one is inherently practicing the instantly claimed methods, as nicotine is delivered into the bloodstream, where it necessarily contacts Aβ protein and inhibits binding of metal ions and/or inhibits aggregation and would necessarily be 'preventing' Alzheimer's disease. Furthermore, because the instant patient population does not preclude smokers or those quitting, any Alzheimer's patient that smokes, or uses the patch, gum, spray or inhaler, is inherently 'treating' and/or 'alleviating' Alzheimer's.

Claims 31-36, 38-42 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by FINDEIS (US Patent5,854,215).

The instant claims are presented *supra.*

Findeis teaches a method of inhibiting Aβ aggregation with compounds of the general formula A-X, A being a 'modulating group' and X being β-amyloid peptide (claim 1), *in vivo* (claim 5), A being a variety of compounds, e.g. acetic acid, fluroescein isothiocyanate (claim 4) and biotin compounds (claim 3), or biotin (e.g. Figure 1).

Findeis additionally teaches treating Alzheimer's with a retro-inverso isomer of Aβ (claim 8), and with Aβ coupled to a modulating group (e.g. claim 38).

Because the compounds meet the structural limitation set forth in the claims and are used in the same method steps, the compound must necessarily have the asserted functions, e.g blocking metal binding, etc.

Conclusion

NO CLAIMS ARE ALLOWED.

The prior art made of record on the attached PTO-892 and not relied upon in any rejection is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571)272-0974. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Andrew D. Kosar, Ph.D.
Art Unit 1654

4/17/06
ANISH GUPTA
PRIMARY EXAMINER

Notice to Comply	Application No. 10031478	Applicant(s) BARNHAM ET AL.	
	Examiner Andrew D. Kosar	Art Unit 1654	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
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